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"DIFFUSE VASCULAR DISEASES"

PART I

There has been a trend in recent years to employ the term peripheral vascular disease or diffuse vascular disease as a catch-all designation for a variety of diseases which are of unknown or uncertain etiology and which exhibit changes in the blood vessels as part of the pathologic process. Some hospitals have established clinics on peripheral vascular disease for the study and treatment of thrombo-angiitis obliterans and circulatory disturbances of the extremities caused by arteriosclerotic occlusion of peripheral arteries. Yet, in the same institutions, internists often use the expression, "peripheral vascular disease," or the term diffuse vascular disease in an entirely different sense; that is, they are used to include suspected cases of periarteritis nodosa, disseminated lupus erythematosus, diffuse scleroderma, and other obscure diseases in which the clinical manifestations suggest the existence of disseminated vascular lesions in the kidneys, retina, muscles, heart or other viscera. Clinicians have found it convenient to use the term "diffuse vascular disease" when a more specific diagnosis cannot be made on clinical grounds and when the exact nature of the pathologic process has not yet been revealed by biopsy of muscle, skin or one of the viscera.

Such a generic term is not objectionable if it is intended to indicate only that a more exact diagnosis is impossible. Unfortunately, its use has led to some confused thinking. The occurrence of vascular lesions in the several diseases mentioned has been hailed as their "common denominator" (Fox). The observation that fibrinoid degeneration of connective tissue represents the primary pathologic change in the walls of the diseased blood vessels has been interpreted as additional support for this viewpoint. The occurrence of fibrinoid degeneration and of vascular lesions in rheumatic fever and rheumatoid arthritis also has been used as an argument to relate these diseases to one another. Finally, the observation of fibrinoid degeneration of connective tissue and vascular changes in the Arthus phenomenon and in serum sickness, which can be reproduced experimentally by the intravenous injection of bacterial and other foreign proteins, has convinced some observers that all diseases in which fibrinoid degeneration and consequent vascular changes occur must, ipso facto, be founded in allergy or hyperergy. This conclusion, and the foregoing premises on which it is based, deserve critical examination.

Fibrinoid Degeneration of Connective Tissues

The term, "fibrinoid degeneration," was introduced by Naumann in 1880. In its descriptive sense (and in the present state of our knowledge this is the only permissible way of using the term) fibrinoid degeneration indicates an alteration of the connective tissues evidenced by swelling and eosinophilia and refractity of its fibers, sometimes accompanied by similar changes in the ground substance. The cellular elements of the connective tissues may participate by proliferation or degeneration, or by a combination of both processes. The occurrence and type of fibroblastic reaction in the areas in which the collagen is altered vary in the several diseases under consideration. Thus, in rheumatic fever, the cellular reaction appears more characteristic than the changes in the noncellular elements. The alterations in the connective tissue vary not only in their qualitative pattern but also in their distribution. In some affections, such as disseminated lupus erythematosus and diffuse scleroderma, they may be found in many tissues and organs of the body; in others, for example, thrombo-angiitis obliterans, periarteritis nodosa and rheumatic fever, they may be limited almost exclusively to the walls of blood vessels.

The term "diffuse collagen disease" was used by Klemperer, Pollack and Baehr to indicate that disseminated lupus erythematosus and diffuse scleroderma were not merely diseases *of* the connective tissue but rather that they were affections of unknown nature in which the damage is often manifest *within* the connective tissues. This does not identify the several diseases, nor does it assume a common or similar pathogenesis.

The occurrence, in experimental and natural hypersensitiveness, of connective tissue changes similar to those seen in rheumatic fever, periarteritis nodosa and disseminated lupus erythematosus has led some authors (Rich and Gregory, and Teilum) to relate all of these diseases to allergy. Although this conclusion *may be* reasonable and possibly even correct in part or in whole, it is not *necessarily* true.

ANNUAL MEETING

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, New Jersey, on June 6th and 7th, 1947. The Hotel President will be the headquarters for all meetings. On June 6th a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association in its relationship to local Heart Associations with particular reference to program. The Annual Meeting of members will also be held on that day. The Scientific Sessions will take place on June 6th and 7th. The Annual Dinner is scheduled for Saturday evening, June 7th at the Hotel President. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

Allergy and Serum Sickness

Gerlach was the first to observe fibrinoid degeneration of collagen in the Arthus phenomenon. Subsequently, Klinge, Roessle, Jaeger and Rich pointed out its occurrence in generalized states of allergy and anaphylaxis of both human beings and experimental animals. Rich and Gregory recently repeated and confirmed the experimental observations of earlier investigators. By intravenous injections of bacterial and heterologous serum proteins, they induced fibrinoid degeneration of connective tissue, vascular lesions and endocarditis. Pathologic lesions have been reproduced which resemble those of periarteritis nodosa and of rheumatic fever.

There is no doubt that fibrinoid degeneration is an essential feature of hyperergic inflammation. This alone does not warrant the assumption that every disease in which foci of damaged collagen and lesions of the vascular system occur are of allergic or hyperergic character. Yet, on this basis, there has been an increasing tendency in recent years to group rheumatic fever, rheumatoid arthritis, periarteritis nodosa, thrombo-angiitis obliterans, disseminated lupus erythematosus, diffuse scleroderma and dermatomyositis in a common "rheumatic" category (Teilum).

It is still necessary to hesitate considerably before accepting this hypothesis. Fibrinoid degeneration of collagen is seen in a variety of conditions which are not even remotely related to allergy. Typical fibrinoid degeneration is found in the walls of arteries in malignant hypertension. It can be reproduced in the arteries of laboratory animals by the Goldblatt procedure, that is, by the artificial reduction in the blood supply of the kidneys. In such experiments there can be no question of allergy.

Fibrinoid degeneration may occur in the base of a peptic ulcer and also in abdominal connective tissue which has been injured by pancreatic ferments released by acute pancreatitis. It may be seen in the reacting connective tissue adjacent to a foreign body. It can be produced experimentally by the local injection into connective tissue of organisms of low virulence and even of chemical agents.

Connective tissue is the supporting and cementing framework of all the organs and tissues of the body. It consists essentially of fibroblasts, collagen laid down in fibrils, and of a ground substance. There is only a limited number of ways in which it can react to injury. It can undergo complete necrosis or, if the injury is less intense, it may undergo degeneration; it may react with cellular proliferation and infiltration; or it may undergo sclerosis. Usually several of these changes occur together, although in varying degrees of intensity. Fibrinoid degeneration may result from any injury to the connective tissue and may occur with or without fibrosis or cellular reaction. It is not specific for any one type of injury.

Periarteritis Nodosa

There is good reason to believe that bacterial or other hypersensitivity is responsible for periarteritis nodosa in many cases. The disease is frequently preceded by attacks of urticaria, asthma or other clinical manifestations of allergy. Marked eosinophilia is usually present at an early stage of the disease, although it may be absent in the later, healing phases of the process and, therefore, may be missed. The characteristic cellular infiltration in the adventitial and medial coats of small arteries is usually, although not invariably, rich in eosinophilic leukocytes. Similar pathologic lesions are found in animals which have been immunized by repeated intravenous injections of bacteria or heterologous proteins, and typical vascular lesions can be reproduced in experimental animals by injections of a sensitizing antigen. Although fibrinoid degeneration of collagen is found in the walls of affected arteries in periarteritis nodosa, it is rarely observed in this disease in connective tissues elsewhere in the body.

Thrombo-angiitis Obliterans

The primary pathologic process in thrombo-angiitis obliterans is a granulomatous inflammatory process in the walls of large arteries of the extremities, followed by occlusion of the lumen. In the more chronic stage of the process, giant cells may be encountered in the midst of the inflammatory tissue. Eosinophils are not conspicuous. The affected tissue of the walls of the diseased vessels may show fibrinoid degeneration.

There is no longer any doubt that Buerger's disease (thrombo-angiitis obliterans) is related to tobacco smoking. Harkavy has demonstrated the presence of reagins to some protein of the tobacco leaf in many sufferers from this disease. Nevertheless, skepticism still exists concerning the role which allergy may play in this disease, because of the direct pharmacologic effect of nicotine and perhaps other ingredients of tobacco smoke on the peripheral circulation. In many people, smoking is promptly followed by pronounced vasospasm and temporary reduction in blood flow through the extremities. Urticaria, asthma, eosinophilia and other clinical phenomena of allergy are not part of Buerger's disease. Thrombo-angiitis obliterans is almost exclusively a disease of males. Conspicuous sex predisposition is not characteristic of any clinically recognizable forms of allergy. The manner in which tobacco smoking induces this disease of the peripheral vessels is, therefore, still obscure.

Rheumatic Fever

The characteristic Aschoff bodies of rheumatic fever are found chiefly in the perivascular connective tissue space of the myocardium, in the connective tissue layer beneath endocardial and serous surfaces, and much less commonly in the walls of arteries. The primary change in the affected locations is necrosis or fibrinoid degeneration of small areas of collagen accompanied simultaneously by a striking and characteristic cellular response. Fibroblastic proliferation is progressive; multinucleated cells (Aschoff cells) appear, and, almost from the beginning, the inflammatory process is associated with the production of new fibrous tissue, especially in the cardiac valves.

In the absence of any other known etiologic agent, rheumatic fever has been suspected of being an allergic response to hemolytic streptococcal infection of the throat, which so often precedes or initiates a recurrence of rheumatic activity in susceptible persons. A complete chain of evidence in support of this hypothesis is still lacking. There is no doubt that exacerbations of the disease, when it already exists in a dormant form, may follow streptococcal infections. On the other hand, exacerbations may occur without a preceding streptococcal sore throat, and even in the absence of hemolytic streptococci in the nasopharyngeal flora. A rise in the streptolysin titer of blood serum is so frequent in rheumatic fever as to be almost diagnostic. Unfortunately, similar rises in antibody titer to nonspecific bacteria occur in other febrile diseases, for example, the Weil-Felix reaction in typhus fever. Rich and Gregory have reported the experimental production of endocarditis and lesions resembling Aschoff bodies by the intravenous injection of heterologous serum proteins. In addition to arthritis and endocarditis, they have produced multiple histologic foci showing fibrinoid degeneration of collagen with marked fibroblastic proliferation. Although these observations are suggestive, it is impossible to be sure that the lesions and the signs of illness observed in the experimental animals are identical with those of rheumatic fever of human beings. In this regard, the previous observation of Friedberg and Gross and of Middleton and McCarter that rheumatic heart disease and periarteritis nodosa not uncommonly occur in association is probably significant.

Rheumatic fever clinically resembles a true infection. The occurrence of multiple cases in the same families suggests cross infections rather than hereditary predisposition to a peculiar "rheumatic" allergy to hemolytic streptococci. Climate and a poor home environment also play too important a predisposing role to warrant accepting bacterial allergy as the explanation for one of the commonest and most crippling febrile illnesses in temperate zones. Until more convincing evidence is available, the allergy theory of rheumatic fever should continue to be regarded with considerable reservation and the search for another etiologic factor should not be halted.

PART II

Disseminated Lupus Erythematosus

In spite of some clinical similarities, disseminated lupus erythematosus can be distinguished clinically and pathologically from rheumatic fever and other diffuse vascular diseases. Disseminated lupus erythematosus is a prolonged febrile disease, sometimes, but not always, characterized by articular pain and erythema. The erythema when present usually appears first on the most exposed parts, the bridge of the nose, malar eminences, the superciliary ridges, the chin, pinna and the V-shaped exposed region over the manubrium. Erythematous macules, often showing telangiectatic capillaries or petechiae, may appear on the tips of the fingers and toes, around the nail bed and scattered on the palms and soles. In extreme cases, the erythema also appears on the parts of the body exposed to friction, the shoulders, elbows, knees and over the malleoli. Profound weakness is always present in this disease. Also characteristic are leukopenia, microscopic hematuria and shallow ulcers on the oral mucous membrane. The disease runs a prolonged course for months or years, with exacerbations and remissions which occur without obvious cause. During exacerbations, pericarditis, pleuritis and endocarditis may occur. Although patients may recover or have partial or complete remissions lasting years, the disease is usually fatal.*

Unlike other diffuse vascular diseases, disseminated lupus erythematosus is predominantly a disease of females; less than 5 per cent of the patients are males. In the absence of the rash, the clinical picture may superficially resemble that of rheumatic fever. The disease should be suspected in any young female who has prolonged fever, asthenia and arthralgia, if leukopenia, microscopic hematuria or vascular lesions in the ocular fundi are present.

The pathologic process in disseminated lupus erythematosus is essentially different from that of rheumatic fever. Fibrinoid degeneration of connective tissue is distributed much more widely throughout the body and is accompanied, as a rule, by little tendency to cellular reaction. The fibrinoid degeneration affects the walls of small arteries, the subendothelial layer of the glomerular capillaries and the subendothelial connective tissues of the endocardium, epicardium and other serous membranes. Even the connective tissue of the mediastinum and retroperitoneum may contain regions in which the interfibrillar ground substance is increased and the collagen fibrils have become so swollen and matted together that they form eosinophilic masses of homogeneous refractive material. When the swelling involves the basement membranes of the glomerular capillaries, the glomerular loops appear discrete and rigid like stiff wire loops. When the process is more severe, the swollen collagenous masses in some loops may be necrotic and superficially resemble the embolic glomerular lesions of subacute bacterial endocarditis.

In affected small arteries, the swollen collagenous material in the media and intima may bulge into the lumen and, in association with desquamation and degeneration of the overlying endothelium, partially or completely occlude the vessel. The vascular lesions which are such a conspicuous and diagnostic part of the clinical picture in disseminated lupus erythematosus are due to these changes in the intramural connective tissue of the affected vessels.

Similar patches of fibrinoid degeneration in the subendothelial connective tissue of the epicardium are responsible for the pericarditis in disseminated lupus erythematosus, those of the pleura are responsible for pleuritis, and those of the peritoneum for perisplenitis or perihepatitis. In the subendothelial connective tissue of the cardiac valves and of the endocardium of the auricles and ventricles, the swollen eosinophilic material may lift up the endothelium and extrude above the surface to form coarse nodular verrucae (Libman-Sacks form of endocarditis). Such verrucae, which are seen microscopically at necropsy in 40 per cent of the cases of disseminated lupus erythematosus, are unlike those of rheumatic endocarditis, both grossly and microscopically. They are usually coarse, and not limited to the line of closure of the valves. Also, unlike rheumatic fever, Aschoff bodies are not found in the myocardium. Although the verrucae on the valves and the walls of the auricles or ventricles adjacent to the valves are free of bacteria, they often have a tendency to become secondarily infected in the last days of the disease (one-third of the cases).

In 60 per cent of the cases of disseminated lupus erythematosus, endocarditis is not visible grossly and only the microscope will reveal areas of change in the subendothelial collagen of the endocardium. Unlike rheumatic fever, murmurs and other symptoms and signs of endocardial or myocardial involvement are usually absent or inconspicuous throughout the entire course of the disease, and the electrocardiogram rarely reveals more than the low voltage seen in any prolonged wasting illness. As a further contrast to rheumatic fever, there is persistent leukopenia, unless a secondary pyogenic infection intervenes, and also, the lymph nodes are enlarged moderately throughout the body. The lymph nodes show hyperplasia and sometimes small or large areas of necrosis which have been mistaken in the past for tuberculosis. The spleen, which is usually enlarged only slightly and, as a rule, is not palpable, has a thick collar of concentrically arranged sclerotic connective tissue fibers around the central arteries.

Although the connective tissue changes of disseminated lupus erythematosus characteristically reveal themselves clinically as vascular lesions (for example, eruption on the skin, microscopic hematuria and vascular lesions of the ocular fundi), all these changes are not invariably present at any one stage of the disease. Occasionally, patients may die after a relatively short fulminating illness in a profound toxic state, and at postmortem examination very little change may be found even microscopically in the viscera.

There is no clinical evidence to support an allergic theory for this disease. It is not preceded or accompanied by bacterial infections, except for secondary invasions in the terminal stage of extreme debility and wasting. It is not associated with urticaria, asthma, eosinophilia or any other clinical manifestations of allergy. Its victims are not especially found among members of atopic families. In spite of the predominant female incidence, no endocrine disorders are evident. Although the Wassermann test is often falsely positive during exacerbations and, as Coburn and Moore have shown, the euglobulin frac-

*A more detailed description of the disease is to be found in Bull. Amer. Heart Assn., Vol. XIII, No. 8, Aug. 1944 (Modern Concepts of Cardiovascular Disease).

tion is sometimes elevated at the expense of the other blood proteins, these are secondary results of the illness and are not present consistently in the early stages. Finally, although fibrinoid degeneration is one of the characteristic features of hypersensitivity inflammation, it is also so readily demonstrable in a variety of nonallergic disease processes that it cannot be accepted, in the absence of any clinical indications, as evidence that disseminated lupus erythematosus is due to hypersensitivity to some unknown agent.

Diffuse Scleroderma

Although the connective tissue changes in the viscera in diffuse scleroderma are identical in distribution and in type with those in disseminated lupus erythematosus, the pathologic changes in the skin and the esophagus are quite different. As in lupus, the skin manifestations begin on the periphery, the hands and feet, bridge of the nose and cheeks, and gradually extend to the rest of the face, extremities and trunk. In diffuse scleroderma, however, the subcutaneous connective tissue undergoes dense sclerosis so that the skin becomes thickened and tight over the bridge of the nose, cheeks and forehead, the mouth becomes puckered and, because of the tightness of the skin on the extremities, the fingers and hands become stiff and fixed in a claw-like position. In extreme cases, immobility of the phalangeal joints and sclerosis of the digital arteries result in severe rarefaction of the phalanges and atrophic destruction of the phalangeal joints, often with extreme atrophy of the epiphyses. Simultaneous degeneration of the capsules of the joints may result in the extensive deposit of calcium into periarticular tissues, so as to form large irregular masses on the phalangeal and metacarpophalangeal joints. A normal concentration of calcium and phosphorus in the blood and the absence of similar deposits of calcium in other parts of the body indicate that these calcareous deposits are merely secondary to local degenerative changes in the connective tissue in and around the phalangeal joints.

Although these progressive changes in the skin at times may be associated with fever of low grade, periods of pyrexia and fulminating illness exhibited by patients with disseminated lupus erythematosus are unusual in diffuse scleroderma unless there are intercurrent infections. Usually, the clinical course is afebrile and slowly progressive for years until death finally occurs because of progressive debility, an inability to swallow due to similar sclerotic changes in the esophagus or an intercurrent pulmonary infection. Temporary arrest in the progress of the disease and even partial remissions without obvious cause are not uncommon. During the course of the disease, attacks of pericarditis and pleuritis may occur and are due to the same collagenous degeneration of the subendothelial connective tissues seen in disseminated lupus erythematosus. As in disseminated lupus erythematosus, microscopic hematuria is commonly observed. The hematuria is due to changes in renal arterioles and glomerular capillaries which are indistinguishable from those of disseminated lupus, including the "wire loop" lesions.

Some patients who have diffuse scleroderma give a history of having experienced Raynaud's phenomenon in the extremities previous to the onset of scleroderma; others do not. Simultaneously with the appearance of thickening and sclerosis of the skin, marked pigmentation of the skin over the extremities and trunk develops in some cases. The pigmentation and the severe asthenia may arouse a suspicion of Addison's disease, especially if the sclerosis of the skin is not yet far advanced. However, the pigmentation in scleroderma does not involve the mucous membranes. Also, the level of the blood sodium and chloride remains normal even when the patient is taking a low sodium or high potassium diet, and the asthenia or the other symptoms of illness are not accentuated by such diets, as they are in Addison's disease. The finding of red blood cells in the urine microscopically also may be of assistance in the differential diagnosis. A biopsy of skin will show sclerosis of connective tissue immediately beneath the epidermis.

Although the lesions in the glomeruli and in the small blood vessels of the kidneys and other viscera and internal tissues of the body consist essentially of fibrinoid degeneration of the collagen and are indistinguishable from those seen in disseminated lupus erythematosus, the changes in the skin and esophagus are diffusely sclerotic from the onset. Even the affected blood vessels of the skin are involved in the dense sclerotic process. This is in striking contrast to disseminated lupus erythematosus in which the skin is soft and extremely vascular and the changes in the subepidermal connective tissue and in affected cutaneous vessels consist of an increase in vascularity and, at most, an increase in ground substance and fibrinoid degeneration of collagen. Sclerosis of connective tissue is encountered in disseminated lupus erythematosus only in the spleen. There it is found in a thick acellular collar of fibers surrounding the central arteries of the malpighian corpuscles. This visceral lesion is not characteristic of diffuse scleroderma.

In spite of the similarity in the collagenous changes in the internal organs in these two diseases, their manner of onset, clinical course and symptomatology are so strikingly different that they bear little or no clinical resemblance. Nor does diffuse scleroderma present the overwhelming predominance among females; the incidence of disease is almost evenly distributed between the sexes. Clinically, they must be considered as examples of two different diseases, in both of which the unknown underlying disturbances exhibit their effects in damage to the connective tissue substrate of the body.

As in lupus, patients with diffuse scleroderma give no clinical, familial or other evidence of any relationship to allergy. An allergic explanation for this disease is clinically as improbable as it is for lupus.

The two diseases (disseminated lupus erythematosus and diffuse scleroderma), together with the other examples quoted in Part I of this paper, provide further evidence that the systemic distribution of fibrinoid degeneration, with its effects on blood vessels and endocardium, and on serous and synovial membranes, is not a specific characteristic of allergic or hyperergic states. In the present state of our knowledge, it is impossible to say more than that the widely distributed lesions seen in these two diseases represent a diffuse injury, of still unknown nature, to the supporting and binding substance of all the organs and tissues of the body, through which the humoral and metabolic exchange between the blood and other tissues takes place.

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